Comments on Amendments to the Specification:

Amendments have been made to the specification to comply with the Examiner's request to respect the proprietary nature of trademarks. The trademarks have been capitalized or inserted where necessary. Several minor, editorial, amendments have been made to correct typographical errors. No new matter has been added. Applicants are unclear, however, on what the Examiner specifically requests by 'accompanying generic terminology.' For example, Triton X-100 is a well-known non-ionic detergent; mere recitation of the name serves to both describe how the invention was performed and describe the reagent used. The same is true of the other trademarked terms used. Applicants are willing to comply with any exact requests of the Examiner but do not wish to add excess, unnecessary verbiage to the specification.

Comments on Amendment to the Claims:

The amendment has been made to address the Examiner's concern under 35 USC § 112 second paragraph that "motif" was unclear in terms of what it encompasses. A conserved amino acid sequence of HCV is at the base of the disclosed invention and is defined throughout the specification. As discussed on page 2, lines 12-19, of the specification, the hypervariable region of E2/NS1 is between amino acids 384 and 410 of HCV. See page 2, lines 12-13. Part of this amino acid sequence has been found to be immunogenic and conserved with respect to the character of the amino acids. See page 2, lines 14-16. Thus, there exists a conserved amino acid sequence within the hypervariable region of E2/NS1. Applicants have amended claims 1 and 7 to specifically point out that the claimed antibody composition contains an antibody capable of binding to the newly

discovered conserved amino acid sequence. Antecedent bases for the amendments are provided throughout the specification: see, e.g., Table 2 on page 30; page 2, lines 25-29; and Example 3 on page 37. As a result of these amendments, Applicants believe that no new matter has been added to the disclosure or the claims and that the claims are neither vague nor ambiguous.

Rejections under 35 USC § 112 first paragraph:

The specification is objected to and Claims 1-12 are rejected under 35 U.S.C. § 112, first paragraph. Applicants respectfully traverse the objection and rejection, and ask that they be reconsidered and withdrawn in light of the remarks made herein.

Several bases for the objection and rejection are provided. In each instance, either the data have been provided, or a standard of evidence is requested which far exceeds the requirements of 35 USC §112, first paragraph. First, the Examiner requests "adequate evidence that the instant application can be used to treat HCV infection in humans." Further evidence of the utility of the chimpanzee model, more chimpanzee experiments and "a statistically significant sample size using appropriate negative controls" is required. Second, the Examiner requests results from all possible antibody-peptide combinations. Third, the Examiner requests data as to the exact epitope recognized by the polyclonal antibody used in the examples. Fourth, the Examiner requests data as to the exact nature of the epitope. Fifth, the Examiner requests data showing that the antibody can be used to treat any HCV strain.

This list of purported deficiencies does not rise to the level needed to support a 35 U.S.C. § 112, first paragraph rejection. Sufficient reasons for doubting the

truth or accuracy of assertions made in the specification must be provided before Applicants are obligated to show evidence supporting the truth or accuracy of the claimed invention. Although, as with all therapeutic compositions, additional testing may be done for years, there is no reason one of skill in the art would doubt the enablement of the claims given the disclosure.

The description is sufficiently detailed to enable a practitioner of ordinary skill in the art to practice the claimed invention. Also disclosed is the best mode known to the Applicants at the time of filing; specifically, an exact sequence of the 7-residue conserved amino acid sequence. (claim 5).

The claimed invention is a method for passive immunization of an individual against Hepatitis C Virus (HCV). The invention is fully enabled by the disclosure. The specification provides a description of how to produce a conserved amino acid sequence from the E2/NS1 antigen of the virus and how to confer passive immunity. The composition used in this method is referred to in this response as a "passive vaccine." There is no evidence that one of skill in the art could not follow the specification to produce the claimed invention.

The broader claims encompass alternative sequences, all of which are expected to be useful for generating a passive vaccine. This expectation is based on several detailed experiments.

Experiment 1: 90 different strains of HCV were isolated, and the amino acid sequence of the E2/NS1 antigen was determined in the appropriate region (Example 1, page 28 and Figure 2). Alignment of the sequences demonstrates that the relevant region of the molecule is hypervariable between

strains. The amino acid sequence provided by the claimed invention is conserved between variants, suggesting that the conserved nature is necessary to support an essential biological function of the protein. The degree of hypervariability elsewhere in the sequence indicates a deliberate mechanism to evade the immune response, so that antibodies against this region will be ineffective in protection. The host species of the variants was human.

In the second part of Experiment 1, variants of the HCV sequence were determined in chronically infected individuals (Example 1, page 28 and Figure 3). To maintain chronicity, HCV viruses continue to vary the sequence of E2/NS1 in response to immunological pressure, creating escape mutants. However, a certain amino acid sequence remains conserved. This further indicates the immunological significance of this region of the antigen. Again, the host species was human.

Experiment 2: Sheep immunized with the conserved amino acid sequence were able to produce antibodies against the sequence (Example 2, page 30, inter alia). This indicates that sources of antibodies for use in producing a passive vaccine can be readily produced. These antibodies are immediately suitable for use in passive immunization. It is not necessary that the antibody of a passive vaccine be of the same species as that being treated: e.g., equine antitoxins against botulism and diphtheria are in current clinical use. If desired, antibodies can be humanized by techniques known and published in the art. Furthermore, the methods in the disclosure for providing the conserved amino acid sequence in an immunogenic form enable antibodies to be raised in any species, including humans.

Experiment 3: Sheep antibodies directed against the conserved amino acid sequence are effective as a passive vaccine (Example 3, page 37, inter alia). This was demonstrated by conferring the sheep antibodies to a chimpanzee, and then challenging the chimpanzee with HCV. The chimpanzee is a preferred animal model for HCV. The dose given was such that viral RNA would otherwise have subsequently been detectable in the serum, along with acute viremia, histological markers, and abnormal liver function tests. The antibodies protected the recipient against all these manifestations of ongoing HCV infection.

Experiment 4: Peptides comprising the conserved amino acid sequence were shown to bind an anti-thyroxin antibody (Example 4, page 42), thyroxin binding globulin, and transthyretin (Example 5, page 42, inter alia). This suggests that the sequence plays a critical role in the binding of HCV to thyroxin-specific proteins as part of the infective process. Consequently, a passive vaccine comprising antibodies against the conserved amino acid sequence will be protective against different strains of HCV, because HCV will not be able to vary the sequence without losing its infectivity.

In light of the existing art, the disclosure is sufficient to overcome the enablement concerns in Paper No. 24. Specific objections of the Examiner are addressed seriatim.

Applicants have provided inadequate evidence that instant invention can be used to treat HCV infection in humans. Applicants have provided no evidence that the chimpanzee model used in the specification predicts efficacy of the instant invention.

The lack of human data is insufficient to establish a rejection under 35 U.S.C. § 112, first paragraph. Section 112 does not require that experimentation actually be performed on human subjects. It has long been established that, enablement has been found where

> one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans. *In re Brana*, 34 USPQ2d 1436, 1442 (CAFC 1995), citing *In re Krimmel*, 130 USPQ 215,219 (CCPA 1961).

The burden does not shift to Applicants to prove that the chimpanzee model predicts efficacy in humans; the Examiner must provide doubt as to the assertions and doubt as to why the data are insufficient to teach "the public that the compound exhibits some desirable pharmaceutical property." Moreover, HCV is a human virus, and the data used to define the conserved amino acid sequence were obtained from strains isolated in humans. Data in Experiment 1 as outlined above show that the conserved sequence is necessarily conserved when HCV infects humans. Experiment 4 explains why this is so. Experiment 3 shows that antibodies against this sequence are protective.

The way in which a passive vaccine protects an individual is an important factor for consideration. Antibodies are provided by a donor to the individual being treated. The immune status of the individual being treated is irrelevant, since he or she acts as a medium in which the HCV and the conferred antibody interact. There is no reason

to believe, and none has been provided to show, that the protective effect observed in Experiment 3 will not also occur in human subjects.

There are obvious ethical considerations in experimentally challenging human subjects with live HCV. Experiment 3 makes use of the only reliable animal model for HCV infection of humans. When the results of Experiment 3 are combined with the data from Experiment 1, there is persuasive evidence for efficacy in humans.

Applicants have not demonstrated in a statistically significant sample size using appropriate negative controls ... that the instant invention can be used for the treatment of HCF infection in chimp[anzee]s.

As noted above, Applicants need only demonstrate "that a compound exhibits some pharmaceutical properties." Applicants have done so and thus need not meet this overly prohibitive interpretation of the requirements of 35 U.S.C. § 112, first paragraph.

Experimental work with HCV is encumbered by the paucity of animal models for what is a essentially a virus specific for higher primates. The chimpanzee is the only reliable model recognized in the field, but it is also an extremely expensive one: the total cost of each animal is greater than $100,000. To insist upon controls and replicates for the purpose of obtaining patent protection in the face of the enormity of the expense would be counter to the public policy objective of patent law, which is to provide incentives for invention and disclosure. See, In re Bundy, 209 USPQ 48 (CCPA 1981).

Negative controls have essentially already been performed, in terms of experience within the art as to the infectivity of HCV in chimpanzees. It is known that the

infective course of HCV is not disturbed by trivial manipulation, such as injection by the excipient that would be comprised in a passive vaccine. The animals would have normal circulating levels of IgG not directed against HCV, and injection with an irrelevant antibody would not significantly alter these levels. As is presently practiced in the art, passive vaccines do not contain any active component other than the specific antibody. (In this way they differ from active vaccines, which also usually comprise an adjuvant.) The negative control suggested by the Examiner is therefore believed to be an unnecessary experiment.

Similarly, the need for repeated experiments is unnecessary. Statistical analysis is required when differences between treated and untreated groups are quantitative only. In this case, the effect of the passively administered antibody was measured qualitatively, and was found to be extremely effective. It is well known that inoculation of chimpanzees with HCV leads to infection of the liver, and is associated with abnormal liver function tests, abnormal liver histology, and overt symptoms. The required dose for infection is well established. While the degree of symptomatology is somewhat variable between individuals, viral replication is inevitable.

The inoculation given in Experiment 3 was 10 times the dose required to confer an infection to an unprotected chimpanzee (page 37, line 28). The PCR test used for analysis after challenge is powerfully sensitive, but failed to detect any signs of ongoing viral replication. Complete protection had therefore been conferred by the passively administered antibodies.

Applicants have provided no evidence that the method of the instant invention can be used to treat chimps that are infected with HCV prior to treatment with the instant invention. The claims as currently written encompass a method which would include the treatment of HCV infected individuals after HCV infection.

Again, Applicants are being asked to provide evidence not necessary to satisfy the requirements of 35 USC § 112, first paragraph. In the absence of a doubt that the invention would function as claimed, Applicants are under no obligation to provide further evidence of enablement. In fact, there is ample evidence to indicate that one of skill in the art would not doubt the scope of enablement.

Passive immunization differs from active immunization in several important respects. One is that active immunization usually requires several weeks or months for an individual to mount an immunological response and thereby express a sufficient quantity of antibody specific to the target. In contrast, in passive immunization, the recipient is instantly conferred with a bolus of antibody, which begins to perform effector activity right after injection.

It is well known in the art that passive immunization is quite effective when given after an infective event. For example, Hepatitis B Immune Globulin is the treatment of choice for a needle-stick injury (see Indications for HBIG in the Physician's Desk Reference). HBIG given within a certain period following infection prevents the virus from entering a replicative state, and thereby prevents the pathologic sequelae that would otherwise occur. Similarly, anti-snake bite venoms are antibody preparations that are clinically administered after a snake bite, to limit the effects of the venom.

[I]t does not appear that the asserted operability of the claimed method of treating HCV would be believable prima facie to persons of skill in the art.

As discussed above, 35 USC § 112, first paragraph, does not require that an invention be believable a priori, merely that one of skill in the art, given the disclosure, would not doubt the scope of enablement. It is incumbent upon the Examiner to provide evidence that one of skill in the art would doubt the truth or accuracy of the claimed invention, in order to establish such a rejection. No evidence has been provided. A mere statement that "it does not appear" to be believable is insufficient to shift the burden to Applicants to establish credibility. On the contrary, in order to provide sufficient disclosure, it is only required that the Applicants teach how to make and use the invention, and that the invention work. Applicants have complied with all these requirements and thus need not provide any evidence that one of skill in the art would believe the invention would work.

Applicants have provided no evidence that any particular antibody against any of these [56,000] different peptides can be used to treat HCV infection in any individual infected with any isolate of HCV.

There is no requirement that each embodiment of an invention be operable and exemplified. In fact, the inclusion of nonoperable embodiments is not a bar to patentability. It is well within the skill of one in the art to determine the efficacy of a particular peptide, given the detailed description, examples and claims. Although for the purpose of supplying a sequence listing, the claimed invention encompasses 56,000 compositions, not all positions in the peptide are relevant to the invention. In

particular, the disclosure teaches that the amino acid residues in positions 4 and 5 in the 6-mer are irrelevant to the conserved sequence (Example 1; see especially Figure 1 and Table 2). The actual number of combinations available is calculable as the product of the possible residues at each of the critical positions (1, 2, 3 and 6). Thus, the maximum number of combinations of the critical residues allowed in claim 1 is 7 x 5 x 2 x 2 = 140. The combinations are further limited in preferred embodiments, as outlined in succeeding claims, as follows:

Claim:	Size of Peptide:	No. of Combinations Possible at Critical Residues
1	6-mer	140
2	7-mer	420
3	6-mer	4
4	7-mer	8
5	7-mer	1

Applicants submit that the number of possibilities embodied by claim 1 are exceedingly conservative for a generic claim. Support for the possible combinations as analogous structures is provided by the data in Figure 2, as summarized in Table 2.

In the absence of a requirement for the Applicants to show that the invention would protect every possible individual against every possible HCV isolate, the requirements of 35 USC § 112, first paragraph, have been

met. Indeed, a 100% efficacy rate is a standard that few pharmaceutical compounds achieve.

Weiner et al. (1992) teach that antibodies against a peptide derived from an HCV infected individual do not bind a second isolate from the same patient. . . . Therefore, it seems unlikely that antibodies against any particular peptide recited in said claims would bind any particular HCV isolate other that a strain with the same amino acid sequence as used to prepare said antibody.

As noted above, Applicants have no obligation to show that antibodies to any peptide would bind to any HCV isolate. It is within the skill of one in the art to make that determination. Moreover, contrary to the Examiner's assertions, Weiner et al. do not teach against the present invention. There is no data provided in the cited reference that indicate the antibodies in the single patient described were directed against the conserved amino acid sequence provided in the claimed invention. In fact, antibodies against this conserved sequence may not naturally occur at effective levels during the usual course of an HCV infection, because HCV is able to evade elimination and propagate between individuals by varying residues outside the conserved sequence. The application discloses interventions that provide antibodies against the critical residues: (a) by active immunization; for example, by forming an immunogen comprised of a peptide comprising the conserved sequence (e.g., page 30 line 23) linked to a mitogen like diphtheria toxoid (page 33 line 9, inter alia) and/or mixed with a standard adjuvant (page 21 line 24, inter alia); and (b) by passive immunization, as in Example 3 and Claims 1-12.

Furthermore, the application discloses utilities for the method of passive immunization beyond that of treating

chronically infected individuals, such as that in the cited reference. In particular, administering the antibodies *before* challenge with HCV, or within a limited period following challenge, would enable elimination of the virus before it gained a replicative foothold in the host and was able to form the escape mutant implied in the cited reference.

[A]pplicant has provided no evidence that all of the . . . peptides encompassed by the formula recited in claims 1 and 2 are immunogenic, and can result in the production of antibodies which bind any strain of HCV.

Section 112 does not require that every possible species of a generic claim be tested. To impose such a requirement undermines the purpose of a generic claim.

> Early filing of an application with its disclosure of novel compounds which possess significant therapeutic use is to be encouraged. Requiring specific testing of the thousands of . . . analogs encompassed by the present claim in order to satisfy the how-to-use requirements of § 112 would delay disclosure and frustrate, rather than further, the interests of the public. In re Bundy, at 52.

Furthermore, it is acceptable that species encompassed by a generic claim have variable efficacy. Even if some of the claimed combinations are inoperative, the claims are not necessarily invalid. Atlas Power Co. v. E.I. Du Pont De Nemours & Co., 224 USPQ 409, 414 (Fed. Cir. 1984). The only requirement is that there be reasonable expectation that species within the genus have the asserted utility. Such reasonable expectation is provided within the present application by the data and explanation provided therein, particularly Experiments 1-3. No evidence has been presented to the contrary.

Applicants have provided no evidence that the antibodies that are responsible for ... said chimp[anzee] were necessarily derived from the peptides recited in claims 1-5 . . . . Furthermore, Applicants have provided no evidence that antibodies against the 30-mer do not recognize a conformation epitope not contained in the peptides recited in claims 1 and 2 . . . Applicants have provided no evidence as to whether said epitope is linear or conformational. Therefore it is unclear as to what region of E2HV could be used . . . other than the intact 30-mer.

The Examiner's assertion that protection may have been provided by antibodies against epitopes including other portions of the 30-mer is speculative, and inconsistent with the data provided. The Examiner is referred to Example 2, a detailed mapping experiment expressly designed to characterized IgG preparations made for passive immunization. Overlapping peptides were synthesized spanning various regions of the 30-mer used to stimulate the antibodies. One of the preparations had activity for VSLLA, from residues 400-404 in the E2HV amino acid sequence. The other preparation had activity for VSLLA (400-404), SLLAPGA (401-407), and LAPGA (403-407) (see page 30 line 25, inter alia and Figure 5). No substantial antibody activity was detected against any portion of the 30-mer outside residues 400-407. The region is nearly identical with that of the conserved sequence, which encompasses residues 401-407.

This IgG was used in Example 3 to confer protection to the chimpanzee against a challenge with HCV. Because all the measurable antibody activity in the preparation was directed against the conserved region, the protective affect is attributable to antibodies against the region.

Applicants have presented no evidence that the antibody used in Example 3 can be used to prevent HCV when the antibody is exposed to any HCV strain other than the strain used in Example 3. It is unclear that the antisera used in Example 3 will bind any HCV strain other than the particular strain used in said experiment.

As discussed above, in the absence of evidence that one of skill in the art would doubt the breadth of the claimed invention, Applicants are not under an obligation to prove operability of each and every embodiment. In fact, the antibody binds to a region conserved in a large number of isolates. This indicates that the antibody would bind this region in other isolates. There is no evidence presented to indicate that the antibody would not bind the conserved region regardless of the isolate to which the region belongs.

Reconsideration and withdrawal of the objection and rejection under 35 USC § 112, first paragraph, are respectfully requested.

Rejection under 35 USC § 112, second paragraph:

Claims 1-12 stand rejected under 35 USC § 112 second paragraph. Claim 1 has been amended to more clearly point out and distinctly claim the invention. Elaboration of the antecedent basis for the amended wording was provided in the earlier discussion of claim amendments. Claims 2-12 depend from claim 1. As a result of the amendment, the rejection under this Section of the title is believed to be overcome. Reconsideration and withdrawal of this rejection is respectfully requested.

Rejection under 35 USC § 103:

Claims 1-12 are rejected under 35 USC § 103 as unpatentable over Ralston et al. (WO 92/08734) in view of Houghton et al. (WO 90/11089). Applicants respectfully traverse the rejection, and request consideration and withdrawal thereof. Establishing unpatentability under USC § 103 requires that the prior art provide some suggestion or teaching of the claimed invention and some indication of success. The prior art makes no mention of the particular conserved region, much less any indication that its use would be successful in generating antibodies which provide immunity. Mere mention of the presence of conserved regions in HCV isolates is insufficient.[1]

Houghton et al. teach how HCV sequences can be used in various diagnostic and therapeutic applications, including the raising of antibodies. As the Examiner points out, Ralston et al. teach that E2 is an important surface antigen likely to be a useful target for effector antibodies. Neither reference gives any indication as to whether any peptides would be effective in generating antibodies for use in passive immunity. Neither reference provides the conserved amino acid sequence in the E2 antigen. This sequence is at the heart of the claimed invention. The

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[1] This is summarized nicely in In re O'Farrell, 7USPQ2d, 1673, 1681 (CAFC 1988):

> The admonition the "obvious to try" is not the standard under §103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. (Citations omitted).

present disclosure teaches residues 401-407 are conserved amongst the 90 HCV strains surveyed and recognized by antibodies which confer passive immunity. Other 6- or 7-amino acid segments of E2 are not conserved between strains.

Without the present disclosure, a practitioner would not necessarily search for a 6- or 7-mer conserved amino acid sequence. Even if one did, he or she would be faced with a Herculean task. Since E2 is hypervariable outside the conserved sequence, an enormous combination of 6 or 7 amino acids would have to be surveyed. There are 64,000,000 possible 6-mers of the genetically encoded amino acids, and 1,280,000,000 7-mers. Truly, "excessive experimentation." Neither reference provides any indication as to which, if any, of these peptides would be suitable for use in generating antibodies which confer passive immunity.

The present disclosure eliminates 99.91% of the possible 6-mers, and 99.99% of the possible 7-mers. The disclosure points the practitioner to a very limited number of combinations at the critical residues, as outlined in the Table provided earlier. This represents a significant advance over the cited prior art.

Reconsideration and withdrawal of the rejection is respectfully requested, as is the allowance of all pending claims.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to our Deposit Account No. 03-1664. However, the Commissioner is

not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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